



Estimated Glomerular Filtration Rate (eGFR) as a Predictor of Outcome after Infrainguinal Bypass in Patients with Critical Limb Ischemia

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KEYWORDS

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Abstract *Objectives:* Renal insufficiency is a risk factor for poor outcome after infrainguinal bypass in patients with critical limb ischemia (CLI). Estimated glomerular filtration rate (eGFR) takes age, gender and body size into account and therefore represents actual renal function more accurately than serum creatinine level alone. The aim of this study was to determine the impact of different stages of renal insufficiency on outcome and to assess the prognostic significance of eGFR in patients with CLI.

Material and methods: 603 patients with CLI who underwent infrainguinal bypass between January 2002 and December 2005 at our institution were included in this retrospective study. We estimated GFR using the Modification of Diet in Renal Disease (MDRD) Study equation. Survival, leg salvage and amputation-free survival were calculated using Kaplan–Meier method. Cox regression analysis was performed to calculate hazard ratios for different outcome variables.

Results: Adjusted hazard ratio (HR) of mortality, limb loss and limb loss and/or death for eGFR <30 ml/min/1.73 m² versus serum creatinine >200 μmol/l was 4.0 (95% CI 2.22–7.39) vs 3.5 (95% CI 1.82–6.84), 6.5 (95% CI 2.71–15.59) vs 6.2 (95% CI 2.47–15.56) and 4.0 (95% CI 2.40–6.63) vs 3.6 (95% CI 2.03–6.25), respectively.

Conclusion: Estimated GFR is better predictor of survival, leg salvage and amputation-free survival than serum creatinine alone. eGFR <30 ml/min/1.73 m² is independent risk factor for all three outcome endpoints.

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Introduction

Cardiovascular mortality is higher among patients with end-stage renal disease (ESRD) compared to normal population.¹ Dialysis dependent patients have usually heavily calcified distal arteries and wound healing is poor due to anemia, malnutrition, impaired immunity and tendency to infection.^{2–5} Thus, patients with ESRD and critical limb ischemia undergoing infrainguinal bypass have poorer post-operative survival and higher amputation rates.^{4,6,7} The impact of mild to moderate renal insufficiency on outcome after arterial reconstructions is less well known. Diabetes mellitus and hypertension are most common underlying causes of renal insufficiency and may further worsen the outcome.^{8–10} However, renal insufficiency per se seems to be independent risk factor for poor prognosis.^{11,12} Chronic inflammatory activity and endothelial dysfunction are found in patients with albuminuria and elevated serum creatinine levels independently of other cardiovascular risk factors and this seems to be associated to progression of atherosclerosis.^{8,13,14}

Measurement of serum creatinine is most commonly used method to assess renal function, but it is an inaccurate estimate of actual renal function, especially in early renal insufficiency.¹⁵ Direct measurement of glomerular filtration rate is the gold standard, but neither inulin clearance nor isotopic methods are practical in clinical use. Glomerular filtration rate can, however, be estimated with serum creatinine based equations; either Modification of Diet in renal Disease (MDRD)¹⁶ or Cockcroft-Gault (CG)¹⁷ formula. These formulas take age, gender, and body size into consideration and are therefore much more accurate in estimating renal function than serum creatinine alone. For example, glomerular filtration rate can in some patients decline to half the normal level before creatinine level reaches the upper limit of normal.¹⁸ There is evidence, that reduced estimated glomerular filtration rate (eGFR) is associated with increased postoperative mortality both after cardiac¹⁹ and other vascular^{20,21} procedures.

The aim of this study was to assess the usefulness of eGFR as a predictor of survival, leg salvage and amputation-free survival after infrainguinal revascularization in CLI patients and, specifically, find out the impact of moderate renal insufficiency on the outcome.

Material and Methods

We retrospectively reviewed our institution's vascular registry (Husvasc). Consecutive 603 patients who underwent infrainguinal bypass for chronic critical limb ischemia (Fontaine class III or IV) between January 1st 2002 and December 31st 2005 at our institution were included in the study. Registry includes patient demographics, comorbid conditions, indications for surgery, specific operative details, complications and outcome at discharge. Follow-up data includes graft patency and dates of any graft revision or graft occlusion and also dates of major amputation or death. Dates of death were retrieved from population registry center. Follow-up visits according to our surveillance programme were at 1, 6, 12 and 24 months. Registry data of all patients included in study were cross-checked

against patient records and any missing data in the registry was retrieved from the patient's records.

Primary end point was major amputation or death. Only amputations above the ankle were considered as major amputations. Serum creatinine (Scr) was measured one day before surgery. Serum creatinine levels were measured using IDMS (isotope dilution-mass spectrometry) traceable enzymatic assay (Roche Diagnostics, Basel, Switzerland), which is one of the most accurate methods available at present.²² Glomerular filtration rate was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation for creatinine results traceable to an IDMS method: $eGFR (mL/min/1.73 m^2) = 175 \times (S_{cr}/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$ (SI units).^{22–24} Chronic kidney disease (CKD) is divided into five stages according to The National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines²⁵ (Table 1). We summed up stages 1 and 2 as well as stages 4 and 5 to establish three categories: eGFR >60 mL/min/1.73 m² (no or mild renal insufficiency), eGFR 30–60 mL/min/1.73 m² (moderate renal insufficiency) and eGFR <30 mL/min/1.73 m² (severe renal insufficiency or renal failure) (Table 1). Comparisons between groups were made using Kruskal-Wallis test for continuous variables and Chi-squared test for categorical variables. Median and interquartile range was also calculated for continuous variables. Serum creatinine was analysed as categorical variable as well by establishing three categories for comparison with GFR, i.e. S-creatinine <120 µmol/L, S-creatinine 120–200 µmol/L, and S-creatinine >200 µmol/L. The lower cut-of value was selected, because it is generally considered the upper limit of normal creatinine value. The upper cut-of value of 200 µmol/L was selected, because values above it represent severe renal insufficiency. Values between these cut-off points represent therefore moderate renal insufficiency.

The median age of study population was 73 years (interquartile range 65–80). The median follow-up time was 5 months (interquartile range 0–46 months). Baseline characteristics and co-morbidities of study population are presented in details in Table 2. Indication was critical limb ischemia in all patients, 40% had rest pain and 60% had ulcer or gangrene. The proportions of femoro-popliteal, crural and pedal bypasses were 181(30%), 261(43%) and 81(13%),

Table 1 Staging of renal insufficiency according to National Kidney Foundation- Kidney Disease Outcomes Quality Initiative (NKF- K/DOQI) guidelines and our modification

Stage	GFR (mL/min/1.73 m ²)	Description	Our modification (GFR and description)
1	≥90	Normal renal function	> 60 no or mild renal insufficiency
2	60–89	Mild renal insufficiency	
3	30–59	Moderate renal insufficiency	30–60 moderate renal insufficiency
4	15–29	Severe renal insufficiency	< 30 severe renal insufficiency or renal failure
5	<15	End stage renal disease (uremia)	

Table 2 Baseline patient characteristics by renal function

Characteristic	All (n = 603)	GFR >60 (n = 366)	GFR 30–60 (n = 176)	GFR <30 (n = 61)	p-value
Age, median (IQ range)	73 (65–80)	72 (64–78)	78 (71–83)	68 (59–78)	<0.0001 ^a
eGFR, median (IQ range)	67 (46–89)	84 (69–103)	46 (38–52)	18 (9–25)	<0.0001 ^a
SCr, median (IQ range)	86 (67–116)	71 (59–83)	116 (97–133)	291 (194–506)	<0.0001 ^a
Male gender	330 (55%)	219 (60%)	73 (42%)	38 (62%)	<0.0001
CAD	359 (63%)	198 (57%)	120 (72%)	41 (71%)	0.002
Diabetes	276 (47%)	154 (43%)	83 (48%)	39 (65%)	0.006
Hyperlipidemia	229 (48%)	139 (47%)	64 (47%)	26 (62%)	0.185
Hypertension	397 (68%)	218 (62%)	133 (78%)	46 (78%)	<0.0001
Current smoking	173 (30%)	125 (36%)	37 (22%)	11 (19%)	0.003
COPD	111 (19%)	63 (18%)	38 (23%)	10 (17%)	0.392
History of TIA/stroke	116 (20%)	69 (20%)	35 (21%)	12 (21%)	0.908
Fontaine class IV	359 (60%)	204 (56%)	116 (66%)	39 (64%)	0.491

IQ = interquartile.

eGFR = estimated glomerular filtration rate.

SCr = serum creatinine.

CAD = coronary artery disease.

^a Kruskal-Wallis test is used for continuous variables and chi-squared test for dichotomous variables.

respectively. 70% of bypass operations were made using autologous vein as graft material.

Kaplan-Meier method was used to calculate cumulative survival, leg salvage and amputation-free survival. Crude hazard ratios (HR) of mortality, limb loss and amputation and/or death were calculated for both eGFR and creatinine using Cox regression analysis. 95% confidence intervals (CIs) for HRs were also calculated. Adjusted hazard ratios with 95 % CIs were also calculated for both eGFR and creatinine. All confounding variables in Table 2 and also location of bypass operation or use of autologous versus other graft material were taken in to this adjusted regression model. HRs were calculated using eGFR and creatinine as continuous and as categorical variables. All statistical analyses were performed using SPSS for Windows, version 13.0 (SPSS inc., Chicago, Ill., USA). *P*-value of ≤ 0.05 was considered as statistically significant.

Results

According to estimated eGFR, 60.7% of patients ($n = 366$) had normal or mildly impaired kidney function (eGFR >60 ml/min/1.73 m²), 29.2% ($n = 176$) had moderate renal insufficiency (eGFR 30–60 ml/min/1.73 m²) and 10.1 % of patients ($n = 61$) had severe renal insufficiency or kidney failure (eGFR <30 ml/min/1.73 m²). However, according to serum creatinine level 77.4% ($n = 467$) had normal renal function (creatinine <120 μ mol/L) and only 15.1% ($n = 91$) and 7.5% ($n = 45$) had moderate (creatinine 120–200 μ mol/L) and severe (creatinine >200 μ mol/L) renal insufficiency, respectively. The incidence of coronary artery disease, hypertension, and diabetes were higher in groups of moderate and severe renal insufficiency compared to those who had normal or just mildly impaired kidney function according to eGFR. There was not statistically significant difference in incidence of hyperlipidemia, COPD, or cerebrovascular disease between groups. eGFR groups were also similar according to Fontaine classification (Table 2). Neither was there statistical difference between groups according to the location of original infra-inguinal bypass

nor according to use of autologous versus other graft material.

Survival, leg salvage and amputation-free survival at one and two years are presented as Kaplan-Meier curves in Figs. 1–3. Adjusted hazard ratio (HR) of mortality, limb loss and limb loss and/or death for eGFR <30 ml/min/1.73 m² versus serum creatinine >200 μ mol/L was 4.0 (95% CI 2.22–7.39) vs 3.5 (95% CI 1.82–6.84), 6.5 (95% CI 2.71–15.59) vs 6.2 (95% CI 2.47–15.56) and 4.0 (95% CI 2.40–6.63) vs 3.6 (95% CI 2.03–6.25), respectively. Both crude and adjusted hazard ratios of mortality, limb loss and amputation and/or death for both eGFR and serum creatinine are presented in Tables 3 and 4.

Discussion

Infrainguinal revascularizations, be those bypass or endovascular, are useless unless limb and life are preserved. Renal insufficiency among other concurrent diseases plays a paramount role in this context. Serum creatinine value has been criticized to be inaccurate to identify mild renal insufficiency.^{15,18} Indeed, in the present study, the number of patients with mild to moderate renal insufficiency was larger when eGFR instead of serum creatinine was used to assess renal function. Low estimated GFR turned out to be the most powerful independent predictor of mid-term death and limb loss. In our series the incidence of diabetes, hypertension and coronary artery disease increased with reduced eGFR, and this is probably one confounding factor. However, diabetes and hypertension are most common underlying conditions of chronic renal insufficiency and CKD patients have higher incidence of advanced atherosclerosis and coronary artery disease.^{8,9} The average follow-up time in our series was only 8 months (median 5 months, range 0–46 months) which was mainly due to very high end point rate: there were 43 deaths per 100 person years and 16 amputations per 100 person years. However, there was also missing follow-up data. The number of patients attending post-operative follow-up visits at 1, 6 and 12 months was 481 (80%), 380 (63%) and 299 (50%), respectively. Patients

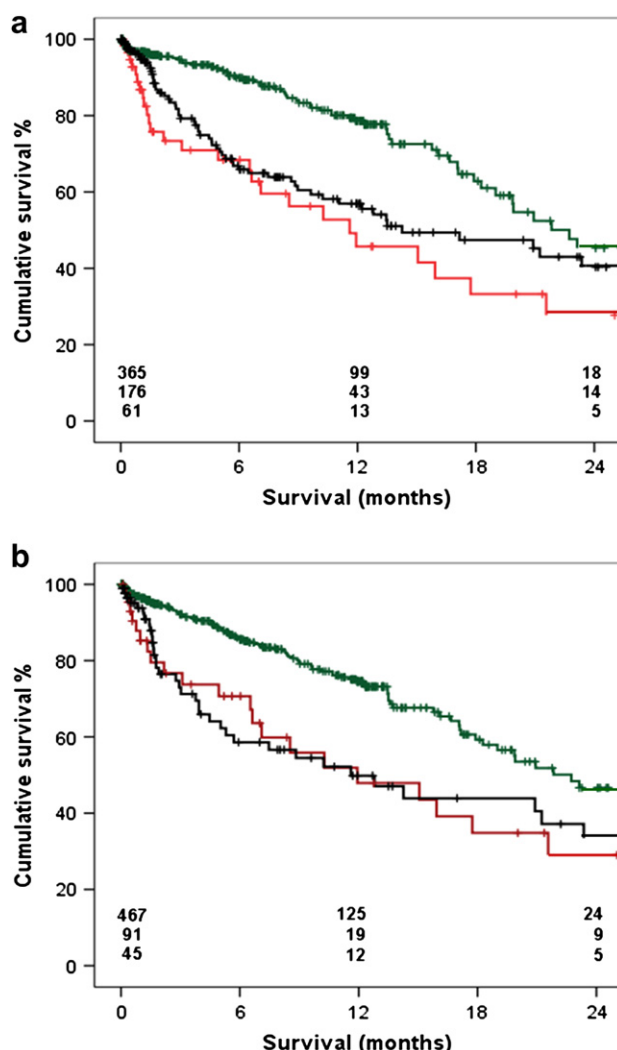


Figure 1 a. One year cumulative survival for eGFR >60 (green line), eGFR 30–60 (black line) and eGFR <30 (red line) is 78.6%, 57.0% and 45.7% respectively. b. One year cumulative survival for Scr >120 (green line), Scr 120–200 (black line) and >200 (red line) is 74.5%, 49.8% and 47.9%, respectively. Numbers above time axis represent patients at risk.

with critical limb ischemia are old and have usually several comorbid conditions, which is probably the main reason we lost patients from our surveillance program.

In recent years only a few authors have published about the association between estimated GFR and survival after infrainguinal bypass. O'Hare *et al.*²⁶ found renal insufficiency to be a strong independent predictor of mortality in CLI patients and that mortality risk was highest among patients with a GFR <30 ml/min/1.73 m². Similarly, GFR <30 ml/min/1.73 m² was a strongly and independently associated with increased risk of death and limb loss in our study. Maithel *et al.*²¹ recently showed, that independent of dialysis status, estimated GFR but not serum creatinine predicted also long term survival after lower limb revascularization. In their series, reduced eGFR was associated to higher mortality up to three years after bypass.

The association of renal insufficiency and increased amputation rate is more controversial. According to O'Hare

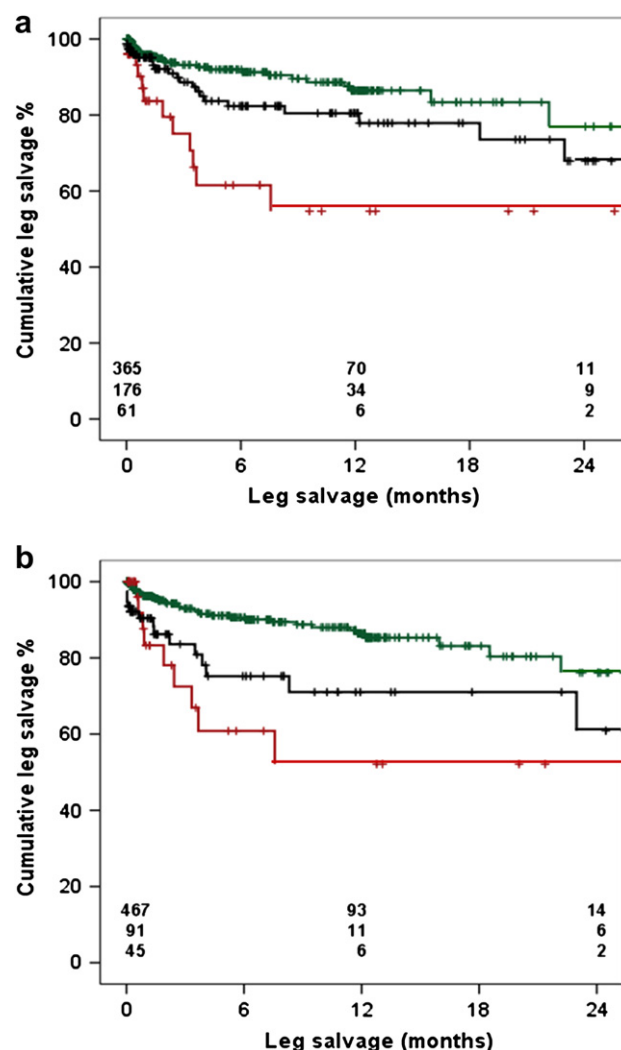


Figure 2 a. One year cumulative leg salvage for eGFR >60 (green line), eGFR 30–60 (black line) and eGFR <30 (red line) is 86.5%, 80.5% and 54.7%, respectively. b. One year cumulative leg salvage for Scr >120 (green line), Scr 120–200 (black line) and >200 (red line) is 86.4%, 71.0% and 52.1%, respectively. Numbers above time axis represent patients at risk.

*et al.*²⁷ dialysis dependent patients, but not patients with milder degrees of renal insufficiency, had high amputation rates. In the same series they found, that 46% of patients receiving dialysis were alive with salvaged leg at 1 year. In our series, eGFR <30 ml/min/1.73 m² was independent predictor of limb loss and death in regression model and only 38.7% of patients with severe renal insufficiency were alive with leg at one year. Also patients with moderate renal insufficiency had higher hazard ratios of limb loss and death and significantly poorer one year amputation-free survival than patients with no or mild renal insufficiency.

Long term amputation-free survival in patients with severe renal insufficiency is poor. Owens *et al.*²⁸ published 49% ± 3% 5-year amputation-free survival for eGFR >30 ml/min/1.73 m² but only 8% ± 4% in patients with eGFR <30 ml/min/1.73 m². Coronary artery disease and poor nutritional status seem to further worsen the outcome of

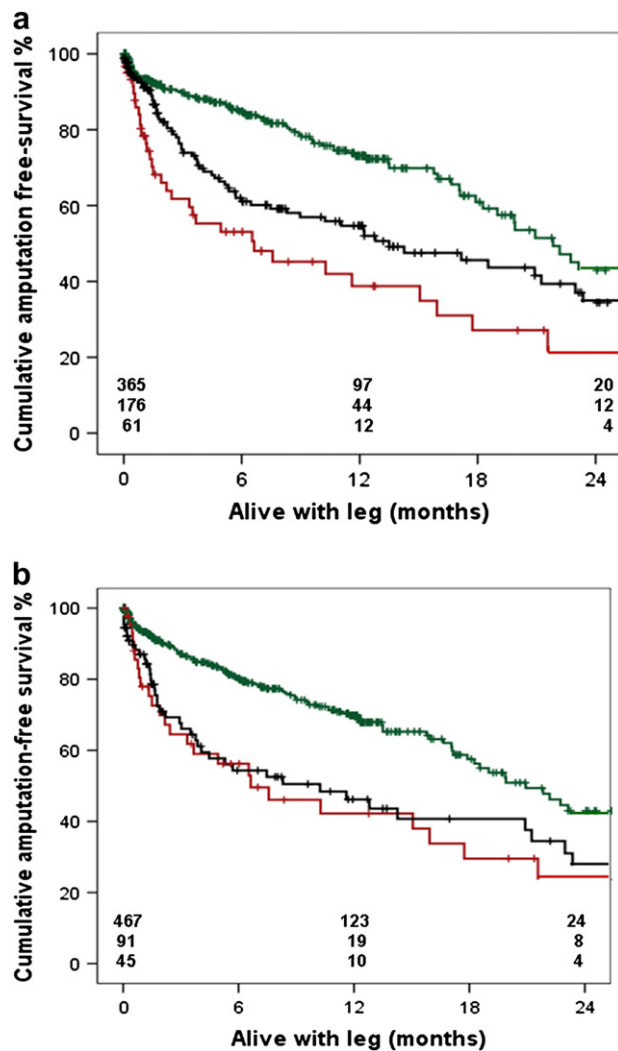


Figure 3 a. One year cumulative amputation-free survival for eGFR >60 (green line), eGFR 30–60 (black line) and eGFR <30 (red line) is 73.2%, 54.7% and 38.7%, respectively. b. One year cumulative amputation-free survival for Scr >120 (green line), Scr 120–200 (black line) and >200 (red line) is 69.8%, 46.2% and 42.2%, respectively. Numbers above time axis represent patients at risk.

dialysis dependent patients. Indeed, earlier data from our institution²⁹ revealed as poor as 12% one year amputation-free survival after infrainguinal revascularization in dialysis depended patients with critical limb ischemia and coronary artery disease. In same series, low serum albumin concentration was also risk factor for poor outcome.

Several studies have showed, that eGFR reflects actual renal function better than serum creatinine alone, but there has also been lot of criticism concerning the use of GFR estimation formulas. A major concern is the accuracy of creatinine assay itself. Due to that it is now recommended that all creatinine methods should become traceable to a reference method based on isotope dilution-mass spectrometry (IDMS). Recalibration of creatinine methods to be traceable to IDMS requires the use of revised MDRD equation with a 6% change in calculation factor from a value of 186 to 175.^{22–24} Both MDRD and Cockcroft–Gault (CG)

Table 3 Crude hazard ratios for different outcome variables

Variable	HR	95% CI	p-value
Survival			
eGFR (continuous)	0.99	0.98–0.99	<0.0001
eGFR (categorical ^a)			
eGFR 30–60	1.80	1.27–2.54	0.001
eGFR <30	2.63	1.69–4.09	0.001
S-creatinine (continuous)	1.00	1.00–1.00	<0.0001
S-creatinine (categorical ^a)			
Scr 120–200	1.90	1.30–2.78	0.001
Scr >200	2.18	1.38–3.45	0.001
Leg salvage			
eGFR (continuous)	0.99	0.98–0.99	0.024
eGFR (categorical ^a)			
eGFR 30–60	1.68	0.95–2.98	0.073
eGFR <30	4.00	2.01–7.97	<0.0001
S-creatinine (continuous)	1.00	1.00–1.01	<0.0001
S-creatinine (categorical ^a)			
Scr 120–200	2.55	1.39–4.69	0.003
Scr >200	3.62	1.74–7.56	0.001
Amputation-free survival			
eGFR (continuous)	0.99	0.98–0.99	<0.0001
eGFR (categorical ^a)			
eGFR 30–60	1.70	1.24–2.34	0.001
eGFR <30	2.83	1.91–4.20	<0.0001
S-creatinine (continuous)	1.00	1.00–1.00	<0.0001
S-creatinine (categorical ^a)			
Scr 120–200	1.89	1.33–2.67	<0.0001
Scr >200	2.31	1.52–3.52	<0.0001

^a For the categorical results the HRs are relative to the baseline renal groups of eGFR >60 or Scr <120.

formulas are developed and validated in populations with CKD. Therefore they are not as accurate in patients without known kidney disease and estimated GFR seems to underestimate actual renal function in patients with normal kidneys.^{30,31} There is also evidence, that these estimating formulas are useful in patients with good nutrition, but they are not as accurate in elderly patients with poor nutritional status.³² CG formula includes weight, and it tends to overestimate the GFR in obese patients. MDRD formula on the other hand overestimates renal function in underweight patients.³³ The advantage of MDRD formula is that patient's weight is not required, which was also the main reason for its use instead of CG formula in this study. There is also some evidence, that MDRD formula may perform better than CG in CKD patients with respect to accuracy.^{33,34} Despite of their limitations, serum creatinine based estimating formulas, such as MDRD, remain the best alternative to assess renal function in every day clinical practise.

Conclusion

Renal insufficiency, not only renal failure, but also moderate impairment of renal function, seems to be a significant risk factor for both limb loss and death after infrainguinal bypass in patients with critical limb ischemia. Low eGFR (<30 ml/min/1.73 m²) is a marker of even higher hazard.

Table 4 Adjusted hazard ratios for different outcome variables

Variable	HR	95% CI	p-value
eGFR(continuous)	0.98	0.98–0.99	<0.0001
eGFR 30–60	1.87	1.22–2.87	0.004
eGFR <30	4.05	2.22–7.39	<0.0001
S-creatinine (continuous)	1.00	1.00–1.01	<0.0001
S-creatinine (categorical ^a)			
Scr 120–200	2.18	1.33–3.59	0.002
Scr >200	3.53	1.82–6.84	<0.0001
Leg salvage			
eGFR (continuous)	1.00	1.00–1.01	<0.0001
eGFR 30–60	1.61	0.78–3.35	0.199
eGFR <30	6.51	2.71–15.59	<0.0001
S-creatinine (continuous)	0.99	0.98–1.00	0.106
S-creatinine (categorical ^a)			
Scr 120–200	2.27	1.01–5.13	0.048
Scr >200	6.20	2.47–15.56	<0.0001
Amputation-free survival			
eGFR (continuous)	0.99	0.98–1.00	<0.0001
eGFR (categorical ^a)			
eGFR 30–60	1.66	1.12–2.47	0.012
eGFR <30	3.99	2.40–6.63	<0.0001
S-creatinine (continuous)	1.00	1.00–1.01	<0.0001
S-creatinine (categorical ^a)			
Scr 120–200	1.82	1.16–2.85	0.010
Scr >200	3.56	2.03–6.25	<0.0001

Both eGFR and Scr are adjusted for age, gender, coronary artery disease, diabetes, hyperlipidemia, hypertension, smoking, COPD, history of TIA or stroke, fontaine class, location of original infra-inguinal bypass operation and use of autologous versus other graft type.

^a For the categorical results the HRs are relative to the baseline renal groups of eGFR >60 or Scr <120.

Regardless of its limitations, estimated GFR is more accurate predictor of survival and leg salvage after infrainguinal bypass in CLI patients than serum creatinine alone. Therefore we conclude, that GFR estimation should be used instead of creatinine level alone in risk evaluation of patients undergoing infrainguinal revascularization for critical limb ischemia.

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